see original article on page 649

Adiponectin: good, bad, or just plain ugly?

Tina Costacou[1] and Trevor J. Orchard[1]

It has been suggested that adiponectin has antiatherogenic, anti-inflammatory, and insulin-sensitizing properties. However, studies in humans have reported inverse as well as positive associations between adiponectin concentrations and disease states. This Commentary discusses the apparent conflict in the literature.

Kidney International (2008) **74**, 549–551. doi:10.1038/ki.2008.262

Since the discovery of adiponectin, much has been said and even more has been hypothesized concerning its role in maintaining health and responding to disease. However, the biologic activities of this adipokine are still not well understood. It is known that adiponectin is a 30-kilodalton polypeptide belonging to the collectin family and is specifically expressed in differentiated adipocytes. It is present in trimer, hexamer, and high-molecular weight forms, whereas a proteolytic cleavage product (known as globular adiponectin) has also been recognized. Although adiponectin isoforms share common effects, they also induce isoform-specific responses, and it has been suggested that high-molecular weight adiponectin confers the vascular-protective activities of this adipokine.[1]

As reviewed recently, antiatherogenic, anti-inflammatory, and insulin-sensitizing properties have been proposed for this molecule.[1] Importantly, studies in human subjects have demonstrated that lower adiponectin concentrations are associated with obesity, severity of insulin resistance, and glucose intolerance,[1] as well as cardiovascular disease among individuals with diabetes, both type 1[2] and type 2.[3] Thus, the observations of markedly elevated concentrations of adiponectin among persons with type 1 diabetes,[4] a state characterized by low-grade inflammation and increased cardiovascular risk, compared with persons with normal glucose tolerance, were somewhat surprising and confusing. Equally surprising were the first cross-sectional findings of increased adiponectin levels in macroalbuminuria compared with states of normal albumin excretion or even microalbuminuria,[5] as renal disease is considered a major risk factor for cardiovascular disease in type 1 diabetes. The observed protective effect of this adipokine for cardiovascular outcomes is thus puzzling, as the same factor appears to render protection against one important outcome, cardiovascular disease, but is positively associated with another important outcome, renal disease.

Nevertheless, a number of potential explanations have been suggested. Failure to establish temporal sequence has often been cited as a justification for the observed cross-sectional adiponectin elevations in macroalbuminuria in these early reports, as levels could potentially increase to counteract harm caused by the disease process. Selective survival is another drawback of cross-sectional designs. However, results of the Mild to Moderate Kidney Disease Study demonstrating that adiponectin was an independent positive predictor of chronic kidney disease progression (defined as a doubling of the baseline serum creatinine and/or terminal renal failure) in 177 patients who completed a 7-year follow-up[6] were also met with confusion, partly because the observed association was restricted to men. Now, the observational study by Jorsal *et al.*[7] (this issue) provides further prospective evidence that elevated adiponectin levels may indeed predict mortality and progression to end-stage renal disease (ESRD) among those with a diagnosis of overt nephropathy in type 1 diabetes. Interestingly, none of the eight common polymorphisms of the *ADIPOQ* gene studied was associated with any of the outcomes, which suggests either the lack of power to detect an association, or that there is indeed no adiponectin-associated genetic predisposition to renal disease progression.

Moreover, although the kidneys possibly play an important role in the biodegradation and/or elimination of adiponectin, recent evidence leads us to believe that altered clearance rates in renal damage are not likely to account for all of the observed increase in adiponectin concentrations in macroalbuminuria. Thus, Chudek *et al.*[8] showed that, despite having decreased from pretreatment levels, adiponectin concentration following transplantation was still twofold higher than the concentration noted among healthy control individuals (15.7 versus 8.7 μg/ml, $P < 0.01$). These results possibly suggest that factors other than renal function influence the regulation of this protein in renal disease, a view further supported by findings of markedly increased adiponectin urinary excretion in individuals with type 2 diabetes and overt nephropathy.[9] It has further been argued that total adiponectin may not be the relevant factor and that its isoforms (especially the high-molecular weight form) should rather be assessed. However, Shen *et al.*[10] recently showed that both total and high-molecular weight adiponectin were elevated in ESRD. Moreover, as in the study by Chudek *et al.*,[8] Shen *et al.*[10] also demonstrated lower levels of total and high-molecular weight adiponectin among those having received a transplant compared with persons with ESRD, although concentrations were still higher than in the control group. Interestingly, the proportion of high-molecular weight to total adiponectin was similar between transplant patients and controls, and lower in these latter groups (transplant patients and controls) than in patients with ESRD.

Consequently, the recent hypothesis that an elevation in adiponectin concentration

[1]*Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA*
Correspondence: *Tina Costacou, University of Pittsburgh, Department of Epidemiology, 3512 Fifth Avenue, Pittsburgh, Pennsylvania 15213, USA. E-mail: costacout@edc.pitt.edu*

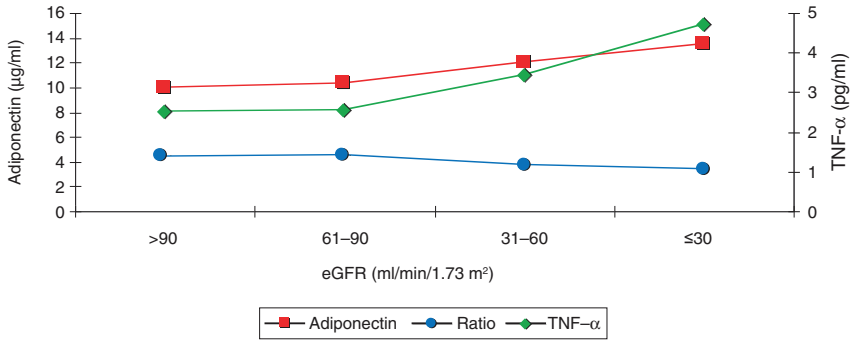

Figure 1 | Adiponectin, tumor necrosis factor-α (TNF-α), and adiponectin-to-TNF-α ratio by estimated glomerular filtration rate (eGFR).

may occur in response to the microvascular damage seen in nephropathy (and other states) certainly appears more attractive, as it could potentially explain the observed inconsistencies. Should this hypothesis hold true, the absolute levels of either total or high-molecular weight adiponectin will prove to be difficult to interpret. A similar situation also exists with regard to another perceived protective factor, high-density lipoprotein cholesterol. Thus, it is possible that whereas low levels of adiponectin and high-density lipoprotein are generally reflective of decreased protection and predictive of increased events, a high level may be reflective of either adequate protection or response to a severe insult, which may in fact be adequate to protect. In all probability, it is in many cases a mixture of both. This is a plausible explanation for the high concentrations seen in high-risk states of this protective factor, as well as the varied results in terms of event prediction ranging from strongly protective to neutral and even strongly positively related to adverse outcomes, as reported by Jorsal *et al.*[7] Indeed, upregulation of adiponectin isoforms and receptor mRNA was recently reported in ESRD.[11]

It seems likely, then, that the conflict in the literature may reflect our inability to paint the complete picture. Although it is widely accepted that organisms have learned to mount a defense against pathogenic insults, typically in epidemiology we tend to ignore this knowledge and study factors associated with disease risk separately from their counterpart factors representing protection or resistance to specific insults. Unfortunately, such assessments may not always accurately represent the processes leading to disease development, and thus it appears critical to simultaneously evaluate not only the risk factor exposure but also the body's (host) reaction. To provide an example of how dramatically different conclusions can be drawn depending on the analytic strategy one follows, we present here previously unpublished data from a small subsample ($n = 108$) of participants in the Epidemiology of Diabetes Complications Study of type 1 diabetes who had a diagnosis of overt nephropathy at study entry. During the 16-year follow-up period, we observed elevations in the concentration of the inflammatory marker tumor necrosis factor-α with worsening of renal function, as estimated by 24-hour creatinine clearance, starting with an estimated glomerular filtration rate (eGFR) less than 90 ml/min/1.73 m^2. Similarly, higher adiponectin concentrations (both total and high-molecular weight adiponectin) were observed with declining eGFR. Despite the latter elevations in adiponectin, however, the ratio of adiponectin to tumor necrosis factor-α (used as a potential marker of response to the increased stress from inflammation) decreased with declining eGFR (Figure 1). These data appear to provide support for the hypothesis that an individual's risk of disease may depend on the individual's ability to counteract stress produced by increased inflammation, and when that response is inadequate relative to the stress, disease progression occurs.

Despite the above cross-sectional and thus speculative data, it is clear that the concurrent evaluation of markers representing, on one hand, insult, and on the other, response to insult, is going to be complex, for a number of reasons. It may not always be known whether a factor represents protection or harm for a given outcome, or even which protective factor is upregulated as a response to which insult. There are literally scores of potential 'stressors' and 'response/defense' factors. Moreover, such strategies may entail the ability to recognize early changes in biomarker interrelationships, and difficulties often exist in establishing when disease initiation occurs, let alone identifying specifically related biomarkers of such early disease stages. Additionally, establishing a definition or characterization of an adequate response to a potential insult may also be challenging, as will consensus on the best statistical methodology to be applied in analyzing such data. Experimental and basic research may be better equipped to more easily address some of the issues raised, although it will take prospective investigations in human populations to reach a full understanding of these complex interactions.

In conclusion, Odyssey or not, this exploratory trip appears to be worth the effort, as the concurrent evaluation of insult and response to insult may lead to novel approaches to identifying both at-risk individuals and also pathways to preventing the progression of insults to full of disease.

DISCLOSURE

The authors declared no competing interests.

REFERENCES

1. Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: a new emerging biomarker of cardiovascular risk. *Pharmacol Res* 2007; **56**: 459–467.
2. Costacou T, Zgibor JC, Evans RW *et al.* The prospective association between adiponectin and coronary artery disease among individuals with type 1 diabetes. The Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia* 2005; **48**: 41–48.
3. Hotta K, Funahashi T, Arita Y *et al.* Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1595–1599.
4. Imagawa A, Funahashi T, Nakamura T *et al.* Elevated serum concentration of adipose-derived factor, adiponectin, in patients with type 1 diabetes. *Diabetes Care* 2002; **25**: 1665–1666.
5. Saraheimo M, Forsblom C, Fagerudd J *et al.* Serum adiponectin is increased in type 1 diabetic patients with nephropathy. *Diabetes Care* 2005; **28**: 1410–1414.
6. Kollerits B, Fliser D, Heid IM *et al.* Gender-specific association of adiponectin as a predictor of progression of chronic kidney disease: the Mild to Moderate Kidney Disease Study. *Kidney Int* 2007; **71**: 1279–1286.
7. Jorsal A, Tarnow L, Frystyk J *et al.* Serum adiponectin predicts all-cause mortality and end stage renal

disease in patients with type I diabetes and diabetic nephropathy. *Kidney Int* 2008; **74**: 649–654.
8. Chudek J, Adamczak M, Karkoszka H *et al.* Plasma adiponectin concentration before and after successful kidney transplantation. *Transplant Proc* 2003; **35**: 2186–2189.
9. Koshimura J, Fujita H, Narita T *et al.* Urinary adiponectin excretion is increased in patients with overt diabetic nephropathy. *Biochem Biophys Res Commun* 2004; **316**: 165–169.
10. Shen YY, Charlesworth JA, Kelly JJ *et al.* The effect of renal transplantation on adiponectin and its isoforms and receptors. *Metabolism* 2007; **56**: 1201–1208.
11. Shen YY, Charlesworth JA, Kelly JJ *et al.* Up-regulation of adiponectin, its isoforms and receptors in end-stage kidney disease. *Nephrol Dial Transplant* 2007; **22**: 171–178.

see original article on page 585

Blocking of angiotensin II is more than blocking of transforming growth factor-β

Christoph Daniel[1]

Fibrosis is a common feature of chronic kidney diseases that is mediated by matrix-producing myofibroblasts. One potential origin of myofibroblasts is epithelial–mesenchymal transition (EMT) of tubuloepithelial cells. Transforming growth factor-β (TGF-β) is a key factor inducing EMT. Carvajal *et al.* demonstrate that angiotensin II induces EMT by classical stimulation of TGF-β and also by a TGF-β-independent pathway, both signaling via Smad molecules. Therefore, blockade of angiotensin II is more than lowering of blood pressure and inhibition of TGF-β stimulation.

Kidney International (2008) **74**, 551–553. doi:10.1038/ki.2008.290

Chronic kidney diseases are emerging as a worldwide public-health problem. Recent reports suggest that up to 10% of the population may be affected by chronic kidney disease (CKD).[1] Irrespective of the underlying cause, CKD is linked with the development of glomerulosclerosis and tubulointerstitial fibrosis, which is the major cause of end-stage renal disease in humans. Fibrosis is characterized by accumulation of matrix molecules such as collagens and fibronectin due to overexpression and decreased clearing and degradation of these matrix components. The key cellular mediator of fibrosis is the myofibroblast, which, when activated, serves as the primary collagen-producing cell.[2] In addition to activated local tissue fibroblasts, myofibroblasts can originate from circulating mesenchymal progenitors or from epithelial cells in a process known as epithelial–mesenchymal transition (EMT).[2] The process of EMT includes disaggregation of epithelial units and reshaping of epithelia for movement. During transition, epithelial cells lose polarity, adherens junctions, tight junctions, desmosomes, and cytokeratin intermediate filaments in order to rearrange their F-actin stress fibers and express filopodia and lamellopodia.[3] Molecular markers of this transition process are, for example, increased expression of vimentin and α-smooth muscle actin and loss of E-cadherin expression.[3] Different cytokines and metalloproteinases have been identified as being involved in the induction of EMT. One key player for EMT induction is transforming growth factor-β (TGF-β). TGF-β promotes EMT by several mechanisms, but the Smad pathway is the most relevant. Additionally, the renin–angiotensin–aldosterone system is a known modulator of renal fibrosis. It is well accepted that angiotensin II (Ang II) induces TGF-β, but less is known about potential TGF−β-independent actions of Ang II on fibrosis and EMT. The article by Carvajal and co-workers[4] (this issue) elucidates an additional role of Ang II in the induction of EMT besides its effects mediated by TGF-β.

This group showed that stimulatory effects of Ang II-induced EMT can be divided in two phases, an early, acute TGF-β−independent and a late TGF-β−dependent phase. Ang II phosphorylated tubuloepithelial Smad2 and Smad3 as early as 24 hours after infusion in rats. At this time point after Ang II infusion, neither TGF-β nor the potential TGF-β activator thrombospondin 1 was increased, suggesting that Smad2/3 phosphorylation is TGF-β independent (Figure 1). In Ang II stimulation experiments using cultured human tubuloepithelial cells, the authors confirmed that Ang II rapidly activates the Smad pathway by a TGF-β−independent mechanism using TGF-β−neutralizing antibody or a TGF-β receptor blocker. Specific blockade of p38–mitogen-activated protein kinase (p38-MAPK), extracellular signal-regulated kinase-1/2 (ERK1/2), and Jun kinase during Ang II stimulation revealed that all three kinases are involved in early activation of the Smad pathway.

This mechanism of TGF-β−independent Smad2 and Smad3 activation by Ang II is not restricted to the kidney. Recent studies using vascular smooth muscle cells (VSMCs) also demonstrated TGF-β−independent Smad activation mediated by MAPK,[5,6] suggesting that this pathway is used in cells of different organs. Interestingly, Smad phosphorylation in VSMCs was mediated by p38[5] or ERK1/2.[6] Although both Smad2 and Smad3 were activated by Ang II by a TGF-β−independent mechanism, only phosphorylation of Smad3 was found to be important for upregulation of collagen I in VSMCs, as was demonstrated by the use of VSMCs defective in either Smad2 or Smad3.[6] For tubuloepithelial cells it is not known whether Smad2, Smad3, or both are required for the induction

[1]*Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany*
Correspondence: *Christoph Daniel, Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Loschgestrasse 8, D-91054 Erlangen, Germany.*
E-mail: Christoph.Daniel@uk-erlangen.de